REMARKS / ARGUMENTS

This amendment is in response to the Office Action mailed on 23 October 2006. Claims 24, 26, 27, 28, 29 and 32 have been currently amended. Claims 25, 30, 31, 33 and 34 have been cancelled. Claims 35 to 38 have been newly added. Accordingly, claims 24, 26-29, 32, and 34-38 are currently presented for Examination. No new matter has been added by this amendment.

Rejection under 35 U.S.C. § 112

The Examiner objects Claim 25 as depending from non-elected claims. Claim 25 has now been cancelled. The Examiner also objected to Claim 25 and 26 as being indefinite and vague. Claim 26 is now redirected to depend on Claim 24 which has been amended to recite "comprising administering modified recombinant human arginase I to a patient, said modification resulting in an extended half-life of said human arginase I of at least 3 days." Applicant believes that Claims 25 and 26 now fully complies with **35 U.S.C. § 112**.

The Examiner also rejects Claim 29, 30 and 33 as being indefinite and vague. Claims 30 and 33 have been cancelled. Claim 29 has now been amended to recite "the method of Claim 28... performed in the absence of protein degradation inhibitor". Applicant submits that the amendment is supported by the PCT specification (see p. 10 line 40-43) and claim 29 complies with **35 U.S.C. § 112**.

Pending claims 25-32 and 34 were rejected by the Examiner as reciting indefinite subject matter. Claims 25, 30, 31 and 34 have been cancelled. Independent claims 24, 28 and dependent claims thereof have been amended to recite "human malignancies" and "modified recombinant human arginase I". Applicant submits that the amendments are supported by the specification and claim 24, 28 and dependent claims thereof complies with **35 U.S.C. § 112**.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejects Claims 24-27 as being anticipated by Vockley et al (US 6316,199). The Examiner asserts that Vockley et al. teach type I human arginase, a method for treating human

cancer by administering arginase polypeptide, recombinant human arginase, a pharmaceutical composition comprising said human arginase with pegylation and a method of treatment without comprising nitric oxide producer.

In view of the Examiner's rejection, Claim 24 has been amended to recite "modified recombinant human arginase I" with "extended half-life of said human arginase I for at least 3 days". Original Claim 27 has been amended to depend on Claim 24 reciting "said [recombinant human] arginase has an extended half-life of at least 6 days in a human having a malignancy". Original Claim 28 has been amended to be an independent claim reciting a method of treatment "comprising administering a pharmaceutical composition that reduces the physiological arginine level in said patient to below 10 μM for at least 3 days."

Applicant would like to point out that according to MPEP section 2131, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Although the Examiner alleges that the Vockley disclosure anticipated Claim 24-27, Applicant does not agree. Applicant would like to explain that Vockley discloses ONLY recombinant human arginase II and its use. In fact, Vockley explicitly aims to clone arginase II for up-regulation of arginase II in hyperargininemia patients (see column 1, line 47 to 49).Vockley clearly shows that hyperargininemia, caused by mutations in the Arginase I gene resulting in severe low level of Arginase I in a human, although significantly devastating, can be compensated by up regulation of arginase II (see Vockley, Background of Invention). The objective of Vockley is to clone the arginase II gene because of its "many potential extra-urea cycle, metabolic roles of arginase II and its up-regulation in the hyperargininemnic patient". Thus no one skilled in the art would have anticipated a method of treatment of **human cancer** with either arginase I or II in a pharmaceutical composition from Vockley's disclosure. Applicant would also like to further explain as follow:

1. Vockley fails to teach modified recombinant human arginase I.

Vockley use Arginase I only as a probe in the cloning and analysis of Arginase II (see col. 34,

line 6 to 7 & col. 11, line 13 to 15). Vockley does not teach any modified recombinant human arginase I, let alone a modified recombinant human arginase with high specificity, high activity and extended half-life (see Example 8C, 9A and 9B). In fact, Vockley teaches how to recover and purify Arginase II from recombinant cell culture, this inherently shows that any proteins/enzymes other than Arginase II is not Vockley's interest (see col. 22, line 62 to col. 23, line 6). Applicant respectfully asserts that one skilled in the art would not be able to anticipate the method of treatment in the present claims.

2. Vockley fails to provide motivation for method of treatment for malignancies.

One skilled in the art before the priority date has already ruled out the possibility of using human arginase I as a pharmaceutical drug. In a 1992 paper, Takaku et al. (Int. J. Cancer 51, 244-249) stated that "Arginase (EC 3.5.3.1) is known to inhibit the growth of various cultured mammalian cells by consuming L-arginine in the culture media, but it has not been applied to the treatment of human cancer because of its poor anti-tumor activity in vivo." [underline added by Applicant.] Takaku further stated that "human liver arginase has a Km value for L-arginine of 10.5 mM. The Km value seems too high to exert enough enzyme activity in human blood, in which the normal L-arginine level is about 0.1 mM. Indeed, its in vivo growth-inhibitory activity is very weak or non-existent." In particular, page 2, line 21 to 34 of instant PCT specification as filed has already shown why arginase was considered at the priority date to be a "dead end" by the skilled person in the art as an effective medicament.

3. Vockley expressly teaches away on the use of recombinant human arginase I for any purpose due to alleged cancer-causing effects.

In Example 8, Vockley down right contradicted the claims of the instant invention. Vockley states that "the elevated arginase activity in the serum is to have a systematic interference with the immune system to include inhibiting lymphocytes and three different splenic derived killer cells. Combined, there is a stimulation of cancer growth while at the same time a local and systematic inhibition of the immune system." Vockley et al. obviously states that elevated arginase activity is a

cause of human cancer, which completely contradicts the method of treatment of cancer in the present application. Based on Vockley's teaching one skilled in the art would turn away from the use Arginase to treat human cancer as it is described as a cancer-causing agent in Vockley.

Thus, Vockley fails to teach a method of treating human cancer using recombinant human arginase I in a pharmaceutical composition.

With reference to the MPEP section 2121.01, "the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." It is insufficient to name or describe the desired subject matter, if it cannot be produce without undue experimentation. The principles underlying application of the criteria of enablement to the content of the prior art were discussed in In re Donohue, 766 F.2d 531, 266 USPQ 619 (Fed. Cir. 1985):

> It is well settled that prior art under 35 U.S.C. 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it is not enabling.

Accordingly, the Vockley patent not only fails to anticipate and teach every single element in the instant application, but also it clearly points away from the present invention. It would not be applicable as 102 prior art. In view of the aforesaid, Applicants respectfully submit that Examiner has not established a prima facie case of 102 anticipation. Applicant respectfully asserts that the amended claims satisfy novelty requirements over Vockley et al. Thus, Applicants request the withdrawal of the rejection based on Vockley and allowance of the pending application.

Rejection under 35 U.S.C. § 103

According to MPEP section 2143, to establish a *prima facie* case of obviousness under 35 U.S.C. 103(a), each of three requirements must be met. First, the reference or references, taken alone or in

combination, must teach or suggest each and every element recited in the claims. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references in a manner resulting in the claimed invention. Third, a reasonable expectation of success must exist.

The Examiner rejects Claims 27, 28-29 and 32-34 as being obvious over Vockley et al. in view of Tepic et al. (US6261557). Claims 27-29 and 32 have been amended accordingly. Claims 33 and 34 were cancelled.

As discussed above, Vockley does not teach a method of treatment of human cancer comprising modified recombinant human arginase I. Vockley also teaches no method of treatment performed in the absence of a protein degradation inhibitor. Therefore Vockley does not teach or suggest each and every element recited in the claims. Furthermore, Vockley explicitly states the elevated serum arginase activity is the cause of human cancer. As discussed above, Vockley provides no motivation for one skilled in the art to produce and use recombinant human arginase I for any purpose due to alleged cancer-causing effects. Thus Vockley is not an applicable 103 prior art.

Tepic on the other hand discloses an extracorporeal method using arginine decarboxylase and protein degradation inhibitor (insulin) to reduce the arginine level in an animal. Applicant respectfully submits that Tepic in combination with Vockley did not teach or suggest every element recited in the amended claims 27-29 and 32. Tepic does not teach to use recombinant human arginase I. Tepic in fact expressly shows that arginine decarboxylase is "the best choice of all known arginine decomposing enzymes. It has a high affinity and specificity for arginine." (see Tepic, Col 8, line 48-50) Tepic in this way discourages one skilled in the art to use recombinant human arginase I. Tepic, in combination with Vockley or any other prior publication, would therefore also discourage one skilled in the art from trying to perform any anti-cancer experiments on human arginase I, and certainly would not have pointed anyone to try to modify arginase I according to the present invention.

Conclusion

In view of the examiner's earlier restriction requirement, Claim 1-23 have been withdrawn. Applicant retains the right to present claims 1-23 in a divisional application. Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early allowance is respectfully requested.

Respectfully submitted,

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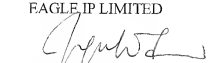

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